The Study of Tumor Volume as a Prognostic Factor in T Staging System for Non-Small Cell Lung Cancer: An Exploratory Study

Bei Jia, MD[1,2,3], Xu Zhang, MD, PhD[1,2,3], Yunxian Mo, MD[2,4], Biao Chen, MD[1,2,3], Hao Long, MD, PhD[1,2,3], Tiehua Rong, MD, PhD[1,2,3], and Xiaodong Su, MD, PhD[1,2,3] [iD]

Abstract

Background: This study aimed to evaluate T staging system for non-small cell lung cancer (NSCLC) using tumor volume (TV) and other prognostic factors. **Methods:** This study included 1309 cases. The TV and greatest tumor diameter (GTD) were semi-automatically measured. The receiver operating characteristic (ROC) curves of TV and GTD were used to predict survival. The regression analysis was used to describe the correlation between GTD and TV. Overall survival (OS) was analyzed using the Kaplan-Meier method. Cox's proportional hazards regression model was applied for multivariate analysis. **Results:** Using the OS in pN0M0 patients (997 cases), we obtained 4 optimal cutoff values and divided all cases into 5 TV groups (V1: TV $\leq$ 2.80 cm^3; V2: TV > 2.80–6.40 cm^3; V3: TV > 6.40–12.9 cm^3; V4: TV > 12.9–55.01 cm^3; V5: TV > 55.01 cm^3) with significant OS (P < 0.001). Multivariate analysis showed that age, visceral pleural invasion (VPI), and all TV cutoff points were independent factors of OS (P < 0.05). For V3 and V4 groups, the OS in patients without VPI was better than that in patients with VPI. Using the values of TV, VPI, and N stages, we classified all cases into 5 stages from I to V depending on the OS. The OS in I, II, III, IV, and V stages were 71.3%, 65.5%, 59.8%, 47.7%, and 35.1% respectively (P < 0.001). **Conclusions:** We proposed a new T staging system using TV as the main prognostic descriptor in NSCLC patients, which may provide a better comprehensive clinical value than GTD in clinical applications.

Keywords

non-small cell lung cancer, tumor volume, greatest tumor diameter, TNM staging system, surgical resection

Abbreviations

1. NSCLC, non–small cell lung cancer; 2. TV, tumor volume; 3. GTD, greatest tumor diameter; 4. OS, overall survival; 5. TNM, tumor node metastasis; 6. UICC, Union for International Cancer Control; 7. CT, computed tomography; 8. MRI, magnetic resonance imaging; 9. SPSS, Statistical package for social sciences; 10. VATS, video-assisted thoracoscopic surgery; 11. VPI, visceral pleural invasion; 12. GGO, ground-glass opacity

Received: June 6, 2020; Revised: July 16, 2020; Accepted: October 23, 2020.

Introduction

Currently, with approximately 1.61 million new cases diagnosed each year all over the world, lung cancer is still the most common cancer.[1] Among all lung cancer cases, non-small cell lung cancer (NSCLC) comprises more than 80%.[2] Although advanced surgical and adjuvant treatment clinical methods are being applied, the prognosis for patients with NSCLC remains poor.[3,4]

Currently, the tumor, node, and metastasis (TNM) staging system, issued by the Union for International Cancer Control (UICC) and American Joint Committee on Cancer (AJCC), is

[1] Department of Thoracic Surgery, Sun Yat Sen University Cancer Center, Guangzhou, People's Republic of China
[2] State Key Laboratory of Oncology in Southern China and Collaborative Innovation Center for Cancer Medicine, Guangzhou, People's Republic of China
[3] Lung Cancer Institute, Sun Yat Sen University, Guangzhou, People's Republic of China
[4] Imaging and Interventional Center, Sun Yat Sen University Cancer Center, Guangzhou, People's Republic of China

Corresponding Author:
Xiaodong Su, Department of Thoracic Surgery, Sun Yat Sen University Cancer Center, 651 Dongfeng Rd. East, 510060 Guangzhou, People's Republic of China.
Email: suxd@sysucc.org.cn

the most significant clinical reference for physicians to make treatment decisions and predict prognosis.[5-8] The latest 8th edition of the TNM staging system that was published in 2017, used more comprehensive data with the purpose of increasing prognostic accuracy for each stage in NSCLC patients.[9] Nevertheless, substantial variations in survival were observed among patients even within the same stage, suggesting that TNM stage alone was not sufficient to be a satisfactory prognostic indicator.[10]

Since the 1970s, the greatest tumor diameter (GTD) has always been one of the most important prognostic factors in TNM staging for lung cancer patients.[11] Admittedly, GTD has its distinct characteristics: it can reflect tumor progression, it is associated with prognosis in patients, and it is convenient to measure. Accordingly, as a cancer descriptor, GTD has held a prominent position for over 50 years.[9] However, many previous studies have proven that GTD may not reflect a real burden of tumor mass accurately, especially in case of irregular tumors.[12-15]

Computed tomography (CT) has been used as one of the standard and non-invasive processes for preoperative staging, treatment evaluation, and prognosis prediction for NSCLC for many years.[16] With the development of imaging technology, the dimensions of tumor volume (TV) can be conveniently acquired and measured using advanced CT software.[17,18] Several previous studies demonstrated that TV was an independent significant prognostic factor in NSCLC patients who underwent curative resection.[19-23] Furthermore, since TV has been proven to have an advantage in reflecting the true tumor burden, previous researchers has suggested that TV influenced the prognosis in NSCLC patients to a greater extent than GTD did.[24,25] However, considering the small sample size or a number of specific stages used in previous studies, the systematic research on the relationship between TV and patient prognosis in the context of the latest staging system has not been well established.

This study aimed to evaluate the prognostic impact of TV as the main index for prognosis in NSCLC patients with stage I to stage III after a complete surgical resection. Furthermore, we aimed to develop a new T staging system that is mainly based on TV.

Materials and Methods

Patients

This research was officially approved by the ethics committee of our center and all patients declared no consents of participating in this study (IRB reference no: B2019-116-01). We retrospectively reviewed 2827 patients with pathologically documented NSCLC at our center from January 1, 2010 to December 31, 2012. Patients were excluded from our data if they didn't undergo curative surgical resection, had other types of cancer, received neo-adjuvant chemotherapy, did not have CT records at our center or had an unmeasurable tumor on CT due to atelectasis, obstructive pneumonia and ground-glass

opacity (GGO) in CT images, were lost of follow-up, or other problems. Finally, we included 1309 patients in this study. The process of cases collection and screening is summarized in Figure 1. The clinical characteristics of patients were collected using a standardized medical data collection form. The initial staging of cases was based on the eighth edition of the TNM Classification for Lung Cancer.[9]

The standard preoperative examinations of NSCLC patients included physical examination, blood test, chest X-rays, chest and abdomen CT, brain magnetic resonance imaging (MRI), bronchoscopy, pulmonary function tests, and electrocardiography.

Lung resection was performed through thoracotomy (Open) or video-assisted thoracoscopic surgery (VATS). The extent of resection included lobectomy, bio-lobectomy, and pneumonectomy. Mediastinal lymph node dissection was performed by surgeons after the lung resection routinely.

TV and GTD Measurement

The contrast enhanced CT images (PHILIP Ict) with section thickness of 1 mm were reviewed by a radiologist blindly using standard lung windows (level −500 HU; width 1500 HU) without knowing the background information of patients. The dimensions for TV and GTD were measured semi-automatically using PHILIPS IntelliSpace Portal v5.0.2.40009 software (Philips Healthcare, Eindhoven, The Netherlands). The software could calculate the TV value automatically after the radiologist outlined the boundary of tumor mass in different imaging dimensions manually (Supplemental Figure).

TV Optimal Cutoff Values

The optimal cutoff TV values were determined using X-tile version 3.6.1 software (Yale University School of Medicine, New Haven, CT, USA) according to the OS of pN0M0 patients.[26]

Follow-Up

All patients accepted follow-up in our out-patient department for at least 5 years after surgery. The standard follow-up process included physical examination, blood test, tumor markers, chest X-ray, chest, and abdominal CT scan. The Overall Survival (OS) was calculated from the date of surgery to the event of death or the date of the last contact.

Statistical Analysis

The receiver operating characteristic (ROC) curves of TV and GTD were used to predict survival, and the values of the area under curves (AUC) were compared using Z test. OS was analyzed using the Kaplan-Meier method and tested using the logrank test. Cox's proportional hazards regression model was applied for multivariate analysis. The Pearson correlation coefficient was used to analyze the correlation between GTD and TV. The regression analysis was used to describe the company

Table 1. The Summary of Patient Clinical Characteristics in the Included Cases.

Characteristic	N	Percent (%)
Total	1309	100
Sex		
Male	926	70.7
Female	383	29.3
Age		
<60	680	51.9
≥60	629	48.1
Smoking		
No	618	47.2
Yes	691	52.8
Type of surgery		
Open	1025	78.3
VATS	284	21.7
Excision site		
Lobectomy	1261	96.3
Pneumonectomy	48	3.7
Central tumor location		
Upper lobe	557	42.6
Middle lobe	153	11.7
Lower lobe	505	38.6
Upper-middle lobe	56	4.3
Middle-lower lobe	38	2.9
Histology		
Adenocarcinoma	737	56.3
Squamous cell carcinoma	387	29.6
Adenosquamous carcinoma	99	7.6
Others	86	6.6
Histologic differentiation		
Poorly differentiated	542	41.4
Moderately differentiated	532	40.6
Well differentiated	235	18.0
Visceral pleural invasion		
No	669	51.1
Yes	640	48.9
Post therapy		
No	986	75.3
Yes	323	24.7
N Stages		
N0	998	76.2
N1	121	9.2
N2	190	14.6

VATS, video-assisted thoracoscopic surgery

relationship between GTD and TV. The linear and non-linear models were tested using F-test, and the coefficients and constants of these models were tested using *t*-test. Statistical analysis was performed using SPSS 23.0.0.0 for Mac system (SPSS Inc., Chicago, IL, USA). If the *P* value (2-tailed test) was less than 0.05, a significant difference was identified in our study.

Results

Clinical Characteristics of Patients

The clinical characteristics of our included 1309 patients are summarized in Table 1. This study included 926 cases of male and 383 cases of female. The cases of N0, N1 and N2 were 998 (76.2%), 121 (9.2%) and 190 (14.6%) respectively.

ROC Curve Analysis

ROC curves showed that values for both AUC of TV and GTD were 0.586 (95% confidence interval [CI]: 0.555–0.617, $P < 0.001$) (Figure 2). This result indicated that survival was correlated significantly with both TV and GTD.

Correlation Analysis of GTD and TV

Our results suggested that the correlation between GTD and TV were in accordance with growth model. The equation for growth model was as follows:

$$lny = 0.636x - 0.059$$

where $y = TV$ and $x = GTD$ (Figure 3).

Optimal Cutoff Values for TV

We used the data of OS in patients to obtain 4 optimal cutoff values based on the pathologically staged pN0M0 tumors (997 cases): 2.80 cm^3, 6.40 cm^3, 12.9 cm^3, and 55.01 cm^3. These cutoff values corresponded to GTD of 1.71 cm, 3.01 cm, 4.11 cm, and 6.39 cm, respectively. Then we divided all patients into 2 subgroups using 2.80 cm^3 as a cutoff value. The OS in patients with TV smaller than 2.80 cm^3 (71.3%) was significantly better than that in patients with TV larger than 2.8 cm^3 (55.0%) ($P < 0.001$). Similarly, the OS in patients with TV smaller than 6.40 cm^3 (67.8%), 12.9 cm^3 (64.8%) and 55.01 cm^3 (59.8%) were obviously better than those with TV larger than 6.40 cm^3 (51.9%), 12.9 cm^3 (50.2%) and 55.01 cm^3 (48.2%) respectively. ($P < 0.001$) (Figure 4).

Group Analysis of OS by TV Cutoff Values

Using 2.80 cm^3, 6.40 cm^3, 12.9 cm^3, and 55.01 cm^3 as cutoff points, we divided pathologically staged pN0M0 patients into 5 groups (V1: TV ≤ 2.80 cm^3; V2: TV > 2.80–6.40 cm^3; V3: TV > 6.40–12.9 cm^3; V4: TV > 12.9–55.01 cm^3; V5 > 55.01 cm^3). The survival rate in each subgroup for pN0M0 patients was 71.3%, 64.8%, 57.2%, 51.3%, and 48.2%, respectively ($P < 0.001$) (Table 2).

### Univariate and Multivariate Analyses of Prognostic Factors for OS

Our results revealed that the prognostic factors in univariate analyses included sex, age, smoking, type of surgery, tumor location, histology, visceral pleural invasion (VPI), all TV cutoff points, and GTD cutoff points (3.0 cm, 4.0 cm, and 5.0 cm). Accordingly, we included these factors into multivariate analysis and results showed that age (Hazard ratio [HR]: 1.482, 95%CI: 1.056–2.081), VPI (HR: 1.632, 95%CI: 1.171–2.274) and all TV cutoff points (2.80 cm^3: HR: 1.692, 95%CI: 0.853–
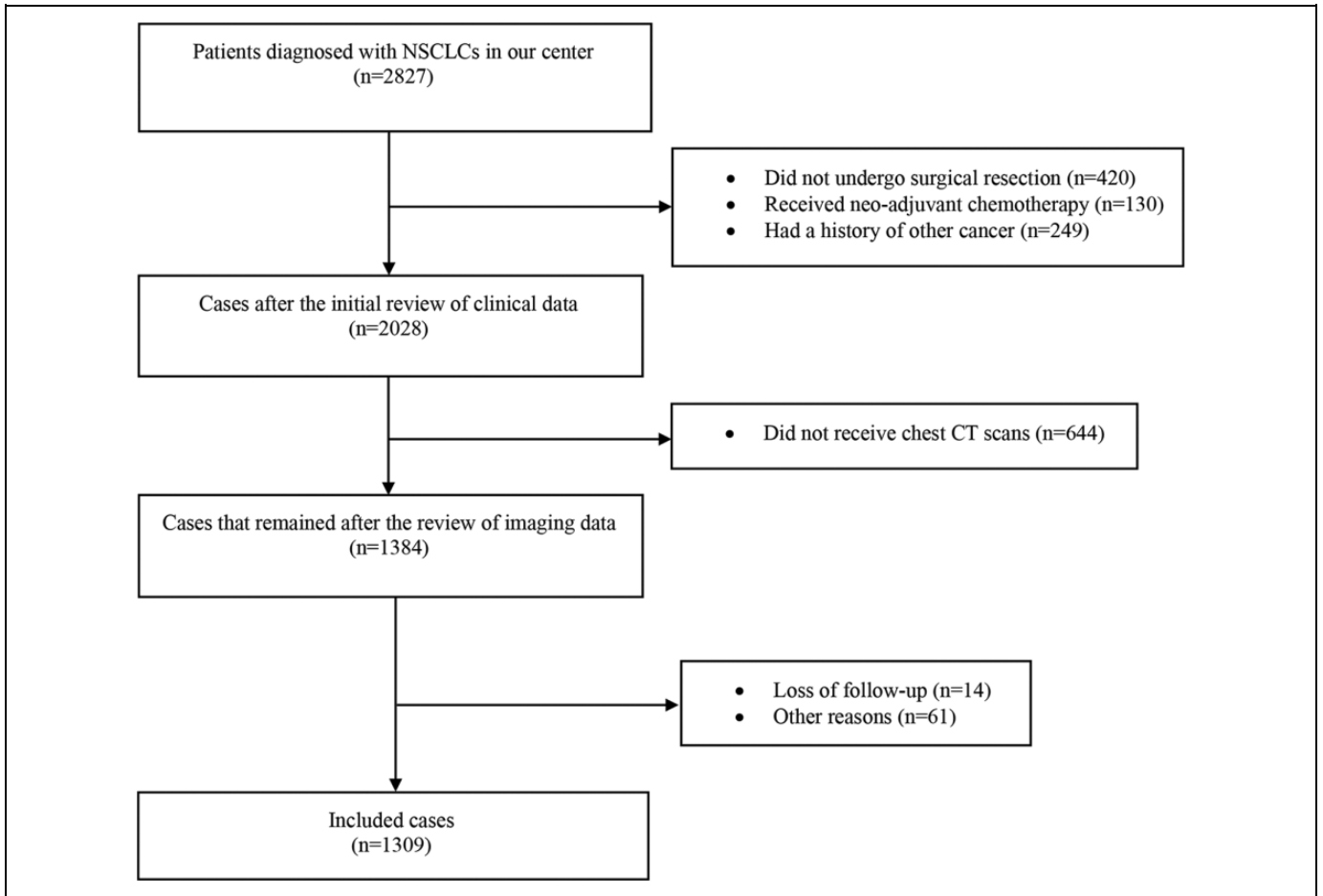
Figure 1. The flow chart of cases collection and screening. Abbreviations: NSCLC, non-small cell lung cancer; CT, computed tomography.
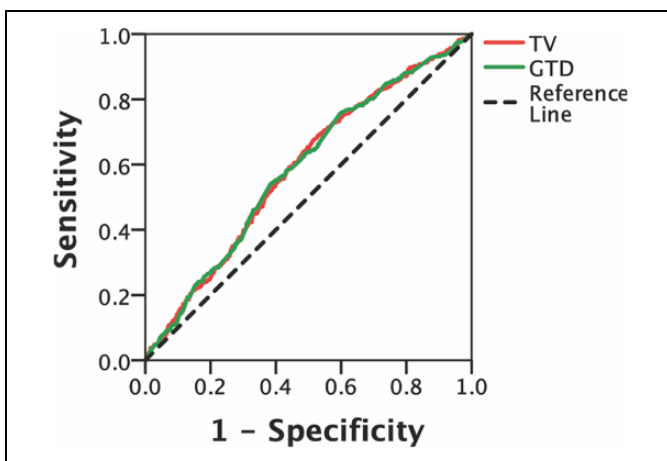

Figure 2. The area under the ROC curves for OS determined using TV and GTD. Abbreviations: ROC, receiver operating characteristic; OS, overall survival; TV, GTD.
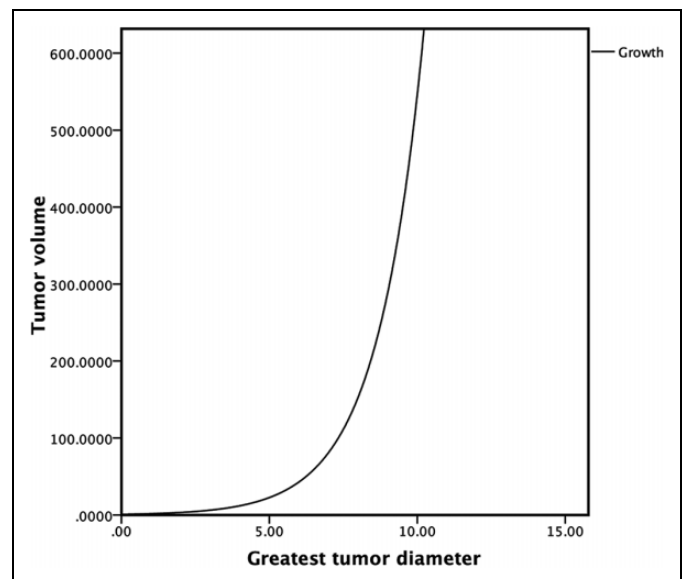
Figure 3. The estimated curve for the correlation between TV and GTD. Abbreviations: TV, tumor volume; GTD, greatest tumor diameter.

2.358; 6.40 cm^3: HR: 1.615, 95%CI: 0.838–3.111; 12.9 cm^3: HR: 0.810 CI: 0.4281.533; 55.01 cm^3: HR: 1.634, 95%CI: 0.886–3.013) were independent factors of OS (Table 3).
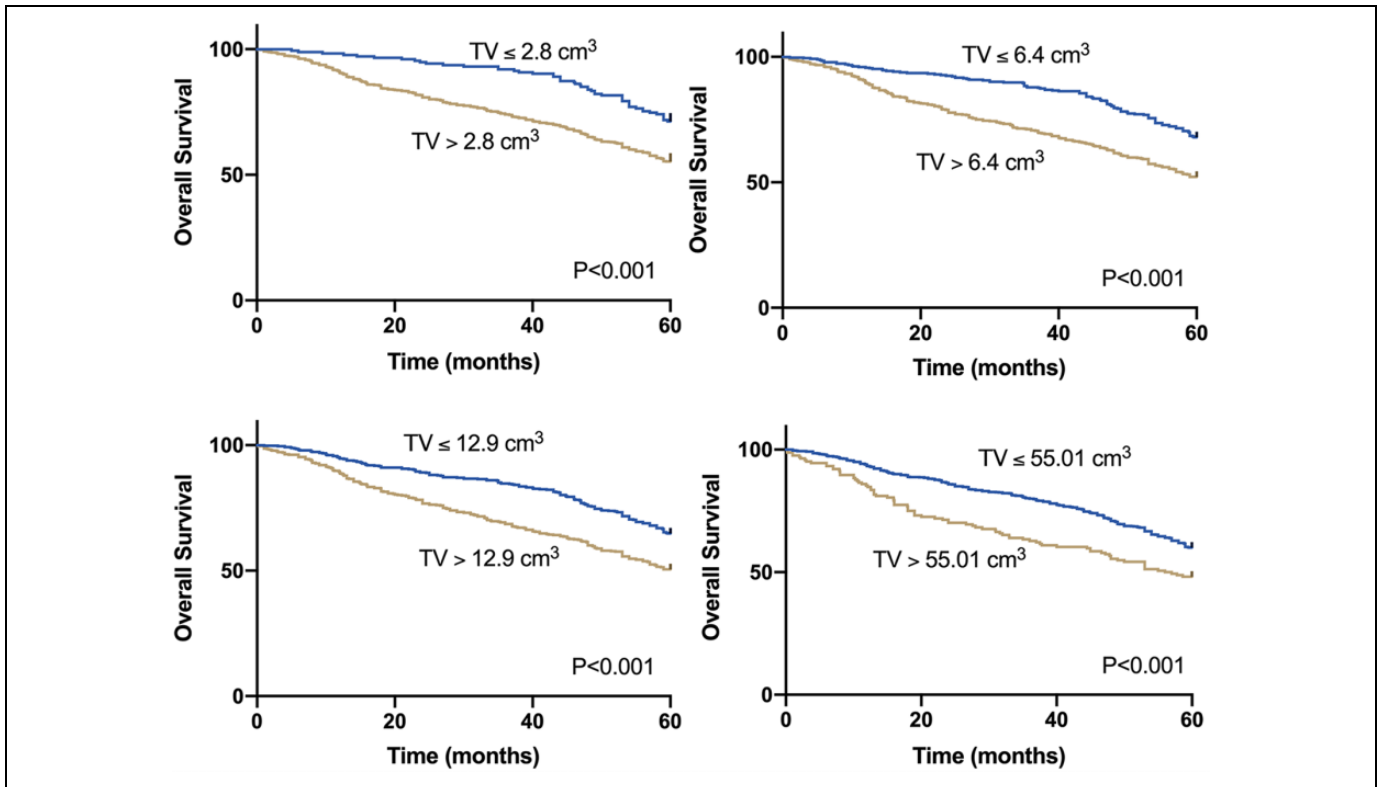
Figure 4. The comparison of OS in pN0M0 patients using the cutoff points of 2.80 cm^3, 6.40 cm^3, 12.90 cm^3 and 55.01 cm^3, respectively. Abbreviations: OS, overall survival.

Table 2. The Analysis of OS by TV Groups With or Without VPI in pN0M0 Cases.

TV groups	OS (%)	OS (VPI -) (%)	OS (VPI +) (%)	P-value
V1: TV≤2.80 cm^3	71.3 (174)	71.8 (110)	70.3 (64)	0.819
V2: TV>2.80-6.40 cm^3	64.8 (199)	65.4 (107)	64.1 (92)	0.700
V3: TV>6.40-12.90 cm^3	57.2 (152)	66.2 (68)	50.0 (84)	0.038
V4: TV>12.90-55.01 cm^3	51.3 (308)	59.6 (151)	47.3 (157)	0.002
V5: TV>55.01 cm^3	48.2 (164)	52.8 (72)	44.6 (92)	0.175

OS, overall survival; TV, tumor volume; VPI, visceral pleural invasion

The Analyses of OS by Presence or Absence of VPI

According to the presence or absence of VPI, we further divided patients in each TV group into 2 subgroups and compared their OS. The results revealed that for V3 group (TV > 6.40–12.90 cm^3), the OS in patients without VPI (66.2%) was significantly better than that in patients with VPI (50.0%) ($P = 0.038$). Similarly, for V4 group (TV > 12.90–55.01 cm^3), the OS in patients without VPI (59.6%) was significantly better than that in patients with VPI (47.3%) ($P = 0.002$). However, we did not observe similar results in other groups ($P > 0.05$). (Table 2)

The Analyses of OS by the Groups Combining TV, VPI and N Stages

In order to further compare the OS using the combined impact of TV and N stages, we divided all patients into 15 subgroups by the different combinations of TV and N stages. In addition, according to the results of VPI mentioned above, we also took VPI as a prognosis factor into consideration for V3N0M0 and V4N0M0 stages. Finally, we had 17 subgroups in total. The survival analysis revealed that there was a similar survival rate in several different subgroups ($P > 0.05$). Therefore, we classified these subgroups into 5 different stages from I to V based on the OS results. The OS of I, II, III, IV, and V stages are 71.3%, 65.5%, 59.8%, 47.7%, and 35.1% respectively ($P < 0.001$). These results are summarized in Table 4 and Figure 5.

The Proposed Staging System According by TV

According to the results shown above, we developed a new T staging system, which is based on TV as summarized in Table 5.

Table 3. The Univariate and Multivariate Analyses of OS in pN0M0 Cases.

				Multivariate analysis	
Characteristic	N	OS (%)	*P*-value	HR (95%CI)	*P*-value
Total	997	57.9			
Sex			<0.001		0.140
Male	713	54.3			
Female	284	66.9			
Age			0.008	1.482 (1.056,2.081)	0.019
<60	511	61.3			
≥60	486	54.3			
Smoking			0.027		0.360
No	471	61.4			
Yes	526	54.8			
Type of surgery			0.009		0.180
Open	787	55.7			
VATS	210	66.2			
Excision site			0.821		
lobectomy	973	57.9			
pneumonectomy	24	58.3			
Tumor location			0.049		0.191
Upper lobe	411	61.3			
Middle lobe	134	53.0			
Lower lobe	406	54.2			
Upper-middle lobe	26	76.9			
Middle-lower lobe	20	70.0			
Histology			0.046		0.957
Adenocarcinoma	541	61.6			
Squamous cell carcinoma	291	50.9			
Adenosquamous carcinoma	95	57.9			
Others	70	58.6			
Histologic differentiation			0.563		
Poorly differentiated	356	56.7			
Moderately differentiated	409	59.2			
Well differentiated	232	57.3			
Visceral pleural invasion			<0.001	1.632 (1.171, 2.274)	0.008
No	508	63.4			
Yes	489	52.1			
Post therapy			0.690		
No	800	57.8			
Yes	197	58.4			
TV subgroups by cutoff points					
TV≤2.80 cm^3 vs TV>2.80 cm^3			<0.001	1.692 (0.853, 2.358)	0.016
TV≤6.40 cm^3 vs TV>6.40 cm^3			<0.001	1.615 (0.838, 3.111)	0.012
TV≤12.90 cm^3 vs TV>12.90 cm^3			<0.001	0.810 (0.428, 1.533)	0.046
TV≤55.01 cm^3 vs TV>55.01 cm^3			<0.001	1.634 (0.886, 3.013)	0.042
GTD subgroups by cutoff points					
GTD≤3.0 cm vs GTD>3.0 cm			<0.001		0.674
GTD≤4.0 cm vs GTD>4.0 cm			<0.001		0.280
GTD≤5.0 cm vs GTD>5.0 cm			0.001		0.810
GTD≤7.0 cm vs GTD>7.0 cm			0.512		

CI, confidence interval; HR, hazard ration; OS, overall survival; TV, tumor volume; GTD, greatest tumor diameter; VATS, video-assisted thoracoscopic surgery.

Discussion

In this study, we used TV as the main index to evaluate the prognosis of NSCLC patients with stage I to stage III after a complete surgical resection. Furthermore, we proposed a new T staging system mainly based on TV. Traditionally, when a tumor was supposed to be a spheroid, pathologic specimen TV was approximately calculated using the formula:

$$TV = (length \times width \times height)/2.^{[27]}$$

However, this conventional method cannot be applied to all types of tumors, especially in the cases of tumors with irregular mass. In this study, using imaging software, we could describe the boundaries of tumor mass more accurately. Therefore, we can acquire the real value of TV to reflect the true tumor burden.

During the past several years, with advances made in imaging technologies, many studies have suggested that TV was a more reliable prognostic predictor than GTD. For stage Ia

Table 4. The Summary of OS Analysis Combining the Obtained From Groups TV, VPI and N Stages.

VNM groups	OS (%)	P-value	OS (%)	P-value
I stage			71.3 (174)	
V1N0M0	71.3 (174)			
II stage		0.981	65.5 (290)	
V1N1M0	66.7 (6)			
V2N0M0	64.8 (199)			
V2N1M0	65.8 (17)			
V3N0M0 (VPI-)	66.2 (68)			
III stage		0.949	59.8 (169)	
V3N1M0	60.1 (18)			
V4N0M0 (VPI-)	59.6 (151)			
IV stage		0.873	47.7 (562)	<0.001
V1N2M0	50.0 (16)			
V2N2M0	48.3 (29)			
V3N0M0 (VPI+)	50.0 (84)			
V3N2M0	48.4 (31)			
V4N1M0	48.9 (47)			
V4N0M0 (VPI+)	47.3 (157)			
V5N0M0	48.2 (164)			
V5N1M0	51.6 (33)			
V stage		0.794	35.1 (114)	
V4N2M0	35.3 (68)			
V5N2M0	34.5 (46)			

OS, overall survival; TV, tumor volume; VPI, visceral pleural invasion
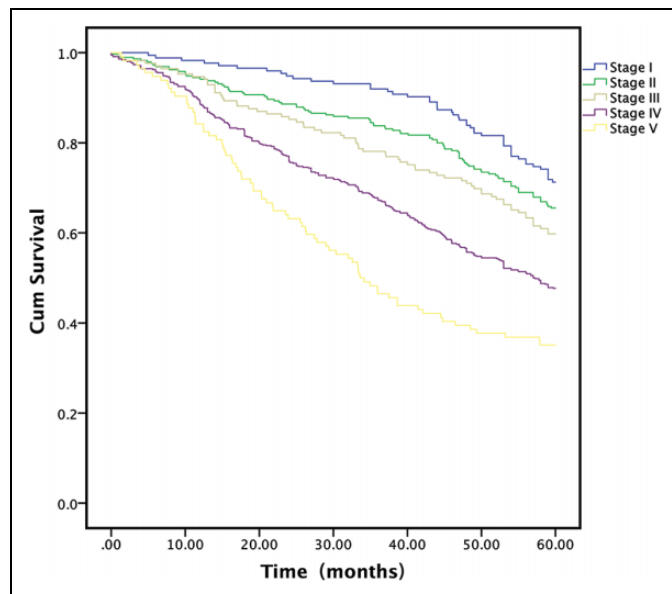
Figure 5. The comparison of OS in total patients based on the new TV staging system of I, II, III, IV and V. Abbreviations: OS, overall survival.

NSCLC, Takenaka et al found that the volume of the tumor solid part was strongly associated with outcome.[21] In addition, Tsai et al analyzed 236 NSCLCs with stage Ia and proposed

Table 5. The Proposed Staging System Incorporating TV Values.

TV groups	N0	N1	N2
V1: TV≤2.80 cm³	I stage	II stage	IV stage
V2: TV>2.80-6.40 cm³	II stage		
V3: TV>6.40-12.90 cm³	II stage (VPI -)	III stage	
	IV stage (VPI+)		
V4: TV>12.90-55.01 cm³	III stage (VPI-)	IV stage	V stage
	IV stage (VPI+)		
V5: TV>55.01 cm³	IV stage		

TV, tumor volume; VPI, visceral pleural invasion

that tumor volume may evaluate tumor size and prognosis more accurately.[27] Our previous study also demonstrated that TV was an independent prognostic factor for stage I NSCLC.[22] For stage II NSCLC, Dai et al suggested that tumor volume >20 cm³ was related to poor outcome in patients. Nevertheless, to the best of our knowledge, most of related studies are limited to one specific stage, and the systemic T staging based on TV has not been well established.

The prognostic significance of tumor volume in nonsurgical therapies have also been confirmed in many previous studies. For adjuvant therapy, Dehing-Oberije et al concluded that in NSCLC patients, tumor volume combined with positive lymph nodes had more prognostic significance than TNM stage.[28] Furthermore, Alexander et al also suggested that current staging systems may not provide a complete information on prognosis in NSCLC patients who underwent chemoradiotherapy; and tumor volume was a better factor to predict outcome for these patients.[29] Furthermore, metabolic tumor volume (MTV), measured by PET-CT, also has been evaluated for its value in the tumor burden as shown by predicting OS and DFS in NSCLC patients.[23,30] Overall, a systematic research on the prognostic value of TV in NSCLC patients is necessary for making clinical treatment projects. Therefore, in the present study, we aimed to evaluate T staging system using TV rather than GTD in stage I-III NSCLC patients after surgical resection.

According to our results, 4 optimal cutoff TV values were obtained using x-tile software. Then, we divided all patients into 5 TV groups based on the significant differences in OS. For pN0M0 cases, both univariate and multivariate analyses of OS in our study revealed that VPI was an independent prognosis factor in pN0M0 patients besides the age and TV cutoff points. VPI, defined as tumor invasion into the visceral pleura elastic layer but not the parietal pleura, has been included in the TNM staging system as one of the T2 descriptors for its significant adverse impact on the prognosis in NSCLC patients.[9]

Therefore, in order to reduce the bias caused by the impact of VPI, for a more accurate evaluation of the prognostic value of TV, we compared the OS in each of the TV groups among patients with or without VPI. We found that the OS in patients without VPI was significantly better than that in patients with

VPI when TV > 6.40-12.90 cm^3 and TV > 55.01 cm^3. According to the growth equation we mentioned before, these TV cutoff points were corresponding to 3.01 cm, 4.11 cm, and 6.39 cm respectively, which we estimated as T2 stage. Similarly, tumors sized between 3.0 and 7.0 cm with VPI were found to be associated with worse prognoses than those without VPI in previous studies.[31,32] Accordingly, in this study we used VPI as an independent upstaging factor in addition to TV and N stages. However, according to the latest edition of the TNM staging system, VPI should not be used to upstage tumors.[33] Considering there are still controversy for the staging value of VPI in NSCLC patients, we believe that our research may provide additional reference in this field.

An accurate prediction of NSCLC patient prognosis preoperatively plays important role for physicians when they decide on appropriate treatment methods. TNM staging system was first published in 1968 and has undergone several modifications during the last 50 years with the advances in understanding in cancer prognosis. GTD, as the main prognostic factor of TNM staging, is still the most recognized indicator to measure tumor mass worldwide.[9] However, there are still many controversial findings related to the latest eighth edition of the staging system.[34-37] Therefore, in this study, we aimed to propose an exploratory T staging system based mainly on TV rather than on GTD. Likewise, our results revealed that different groups defined by the combined impact of TV, VPI, and N stages, can be classified into several stages based on the OS. In our study, all cases can be classified into 5 stages in total. Similar to the relationship between GTD and survival, our results revealed that larger TV is also associated with poorer prognosis. The main reason for this phenomenon may be that tumors with larger TV accompanied with greater tumor burden, which have more risk of lymphatic metastasis and distant metastasis for NSCLC patients.[38,39] Nevertheless, compared with the latest TNM staging system, our staging system based on TV, provided different classification depending on different OS. The most important reason for this difference is that we used TV as a main descriptor for OS with its natural differences with GTD.

Currently, with more and more pulmonary nodules that are being detected using imaging technologies, the need for lymph nodes dissection is still under a debate for this group of cases.[40-42] The main reason for this lack of consensus is the discrepancy between the irregular shapes of different tumor masses, even among those with the same sizes.[22] In the other words, GTD is not sufficient to reflect tumor burden. According to our TV staging system, the survival of patients with N0-N2 in V1-V3 groups, respectively, was different, which indicates that the lymph nodes dissection should be applied routinely for the cases of small tumor after lobectomy. Accordingly, our findings may have clinical value for surgeons to choose proper operative methods based on lymphatic status.

With the wide use of CT and 3D reconstruction technology, the precise and convenient TV measurements will be more and more available for clinical physicians. Comparing with traditional T staging system, we believe that a new T staging system based on TV may provide more valuable reference for surgeons

to choose treatment projects and predict survival in NSCLC patients preoperatively, and our research can contribute to the prevalence and application of TV as the main clinical prognosis factor in the future.

Several limitations should be mentioned in this study. Firstly, it was a retrospective study with its respective potential biases. Secondly, we used OS as the indicator of prognosis, and patients received various postoperative adjuvant treatments such as chemotherapy and radiotherapy. Therefore, the outcomes of OS analysis may have been affected by these factors. Thirdly, considering the limited data available in our medical records, we did not include other factors such as metastasis and N3 stage as staging descriptors in this study. Therefore, this is an exploratory T staging system based on TV and more comprehensive data from multiple centers are needed for further research to verify our findings.

In summary, we proposed a T staging system using TV as a main prognostic descriptor for NSCLC patients. Since TV can reflect tumor burden more accurately than GTD, this exploratory staging system may provide a more comprehensive clinical value than GTD for making optimal treatment decisions and predicting survival. Besides, as a new systematic T staging system based on TV, our findings may provide valuable references for further study of this field.

Authors' Note

Co-first author: Bei Jia, Xu Zhang, Yunxian Mo. This research was officially approved by the ethics committee of Sun Yat sen University Cancer Center and all patients declared no consents of participating in this study (IRB reference no: B2019-116-01).

Acknowledgments

Declaration of Conflicting Interests

Funding

ORCID iD

Xiaodong Su https://orcid.org/0000-0001-8771-5022

Supplemental Material

Supplemental material for this article is available online.

References

1. Parkin DM, Bray FI, Devesa SS. Cancer burden in the year 2000. The global picture. *Eur J Cancer*. 2001;37(suppl 8):S4-S66.

2. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer*. 2015;136(5):E359-E386.

3. Torre LA, Siegel RL, Jemal A. Lung cancer statistics. *Adv Exp Med Biol*. 2016;893:1-19.

4. Miller KD, Siegel RL, Lin CC, et al. Cancer treatment and survivorship statistics, 2016. *CA Cancer J Clin*. 2016;66(4):271-289.

5. Spira A, Ettinger DS. Multidisciplinary management of lung cancer. *N Engl J Med*. 2004;350(4):379-392.

6. UyBico SJ, Wu CC, Suh RD, Le NH, Brown K, Krishnam MS. Lung cancer staging essentials: the new TNM staging system and potential imaging pitfalls. *Radiographics*. 2010;30(5):1163-1181.

7. van Rens MT, de la Riviere AB, Elbers HR, van Den Bosch JM. Prognostic assessment of 2,361 patients who underwent pulmonary resection for non-small cell lung cancer, stage I, II, and IIIA. *Chest*. 2000;117(2):374-379.

8. Adebonojo SA, Bowser AN, Moritz DM, Corcoran PC. Impact of revised stage classification of lung cancer on survival: a military experience. *Chest*. 1999;115(6):1507-1513.

9. Detterbeck FC, Boffa DJ, Kim AW, Tanoue LT. The eighth edition lung cancer stage classification. *Chest*. 2017;151(1): 193-203.

10. Goldstraw P, Chansky K, Crowley J, et al. The IASLC lung cancer staging project: proposals for revision of the TNM stage groupings in the forthcoming (Eighth) edition of the TNM classification for lung cancer. *J Thorac Oncol*. 2016;11(1):39-51.

11. Mountain CF. Revisions in the international system for staging lung cancer. *Chest*. 1997;111(6):1710-1717.

12. Jennings SG, Winer-Muram HT, Tarver RD, Farber MO. Lung tumor growth: assessment with CT—comparison of diameter and cross-sectional area with volume measurements. *Radiology*. 2004;231(3):866-871.

13. Ball DL, Fisher R, Burmeister B, et al. Stage is not a reliable indicator of tumor volume in non-small cell lung cancer: a preliminary analysis of the Trans-Tasman Radiation Oncology Group 99-05 database. *J Thorac Oncol*. 2006;1(7):667-672.

14. Zhao B, Schwartz LH, Moskowitz CS, Ginsberg MS, Rizvi NA, Kris MG. Lung cancer: computerized quantification of tumor response—initial results. *Radiology*. 2006;241(3):892-898.

15. Suzuki C, Jacobsson H, Hatschek T, et al. Radiologic measurements of tumor response to treatment: practical approaches and limitations. *Radiographics*. 2008;28(2):329-344.

16. Aberle DR, DeMello S, Berg CD, et al. Results of the two incidence screenings in the national lung screening trial. *N Engl J Med*. 2013;369(10):920-931.

17. Scholten ET, de Hoop B, Jacobs C, et al. Semi-automatic quantification of subsolid pulmonary nodules: comparison with manual measurements. *PLoS One*. 2013;8(11):e80249.

18. Gietema HA, Wang Y, Xu D, et al. Pulmonary nodules detected at lung cancer screening: interobserver variability of semiautomated volume measurements. *Radiology*. 2006;241(1):251-257.

19. Dai Y, Su XD, Long H, et al. Survival analysis of 220 patients with completely resected stage-II non-small cell lung cancer. *Chin J Cancer*. 2010;29(5):538-544.

20. Lee JW, Lee SM, Yun M, Cho A. Prognostic value of volumetric parameters on staging and posttreatment FDG PET/CT in patients with stage IV non-small cell lung cancer. *Clin Nucl Med*. 2016; 41(5):347-353.

21. Takenaka T, Yamazaki K, Miura N, Mori R, Takeo S. The prognostic impact of tumor volume in patients with clinical stage IA non-small cell lung cancer. *J Thorac Oncol*. 2016;11(7):1074-1080.

22. Su XD, Xie HJ, Liu QW, Mo YX, Long H, Rong TH. The prognostic impact of tumor volume on stage I non-small cell lung cancer. *Lung Cancer*. 2017;104:91-97.

23. Kumasaka S, Nakajima T, Arisaka Y, et al. Prognostic value of metabolic tumor volume of pretreatment (18)F-FAMT PET/CT in non-small cell lung cancer. *BMC Med Imaging*. 2018;18(1):46.

24. Mozley PD, Schwartz LH, Bendtsen C, Zhao B, Petrick N, Buckler AJ. Change in lung tumor volume as a biomarker of treatment response: a critical review of the evidence. *Ann Oncol*. 2010; 21(9):1751-1755.

25. Zhao B, Oxnard GR, Moskowitz CS, et al. A pilot study of volume measurement as a method of tumor response evaluation to aid biomarker development. *Clin Cancer Res*. 2010;16(18): 4647-4653.

26. Camp RL, Dolled-Filhart M, Rimm DL. X-tile: a new bioinformatics tool for biomarker assessment and outcome-based cut-point optimization. *Clin Cancer Res*. 2004;10(21):7252-7259.

27. Tsai CH, Lin CM, Hsieh CC, Hsu WH, Wang HW, Wang LS. Tumor volume is a better prognostic factor than greatest tumor diameter in stage Ia non-small cell lung cancer. *Thorac Cardiovasc Surg*. 2006;54(8):537-543.

28. Dehing-Oberije C, De Ruysscher D, van der Weide H, et al. Tumor volume combined with number of positive lymph node stations is a more important prognostic factor than TNM stage for survival of non-small-cell lung cancer patients treated with (chemo)radiotherapy. *Int J Radiat Oncol Biol Phys*. 2008;70(4): 1039-1044.

29. Alexander BM, Othus M, Caglar HB, Allen AM. Tumor volume is a prognostic factor in non-small-cell lung cancer treated with chemoradiotherapy. *Int J Radiat Oncol Biol Phys*. 2011;79(5): 1381-1387.

30. Kim K, Kim SJ, Kim IJ, Kim YS, Pak K, Kim H. Prognostic value of volumetric parameters measured by F-18 FDG PET/CT in surgically resected non-small-cell lung cancer. *Nucl Med Commun*. 2012;33(6):613-620.

31. Shimizu K, Yoshida J, Nagai K, et al. Visceral pleural invasion is an invasive and aggressive indicator of non-small cell lung cancer. *J Thorac Cardiovasc Surg*. 2005;130(1):160-165.

32. Yoshida J, Nagai K, Asamura H, et al. Visceral pleura invasion impact on non-small cell lung cancer patient survival: its implications for the forthcoming TNM staging based on a large-scale nation-wide database. *J Thorac Oncol*. 2009;4(8):959-963.

33. Rami-Porta R, Bolejack V, Crowley J, et al. The IASLC lung cancer staging project: proposals for the revisions of the T descriptors in the forthcoming eighth edition of the TNM classification for lung cancer. *J Thorac Oncol*. 2015;10(7):990-1003.

34. Chen T, Luo J, Gu H, et al. Should minimally invasive lung adenocarcinoma be transferred from stage IA1 to stage 0 in future updates of the TNM staging system? *J Thorac Dis*. 2018;10(11): 6247-6253.

35. Wang S, Zhang B, Qian J, et al. Proposal on incorporating lymphovascular invasion as a T-descriptor for stage I lung cancer. *Lung Cancer*. 2018;125:245-252.

36. Samejima J, Yokose T, Ito H, et al. Prognostic significance of blood and lymphatic vessel invasion in pathological stage IA lung adenocarcinoma in the 8th edition of the TNM classification. *Lung Cancer*. 2019;137:144-148.

37. Zhang T, Zhang JT, Li WF, et al. Visceral pleural invasion in T1 tumors (</=3 cm), particularly T1a, in the eighth tumor-node-metastasis classification system for non-small cell lung cancer: a population-based study. *J Thorac Dis*. 2019;11(7): 2754-2762.

38. Liu J, Dong M, Sun X, Li W, Xing L, Yu J. Prognostic value of 18F-FDG PET/CT in surgical non-small cell lung cancer: a meta-analysis. *PLoS One*. 2016;11(1):e0146195.

39. Zhang C, Liao C, Penney BC, Appelbaum DE, Simon CA, Pu Y. Relationship between overall survival of patients with non-small cell lung cancer and whole-body metabolic tumor burden seen on postsurgical fluorodeoxyglucose PET images. *Radiology*. 2015; 275(3):862-869.

40. Yu Y, Jian H, Shen L, Zhu L, Lu S. Lymph node involvement influenced by lung adenocarcinoma subtypes in tumor size </=3 cm disease: a study of 2268 cases. *Eur J Surg Oncol*. 2016;42(11): 1714-1719.

41. Shi CL, Zhang XY, Han BH, He WZ, Shen J, Chu TQ. A clinicopathological study of resected non-small cell lung cancers 2 cm or less in diameter: a prognostic assessment. *Med Oncol*. 2011;28(4):1441-1446.

42. Zhang YK, Chai ZD, Tan LL, et al. Association of lymph node involvement with the prognosis of pathological T1 invasive non-small cell lung cancer. *World J Surg Oncol*. 2017;15(1):64.